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### HAVE YOU READ?

## What is the Urologist to do in a BCG Shortage?



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Treatment of nonmuscle invasive bladder cancer (NMIBC), comprising the majority of bladder cancer cases, remains complex. Prior studies have validated the clinical benefit of bacillus Calmette-Guérin (BCG) in reducing disease recurrence and progression. The typical induction

course of BCG consists of 6 weekly instillations and is recommended by the AUA.<sup>1</sup>

Level 1 evidence supports the use of maintenance BCG beyond the 6-week induction course. Best practice supports the SWOG (Southwest Oncology Group) protocol of 3

weekly instillations at 3, 6, 12, 18, 24, 30 and 36 months from the initiation of induction therapy.<sup>2</sup> Based on findings from EORTC (European Organisation for the Research and Treatment of Cancer) 30911, even in intermediate risk patients, 3-week maintenance BCG significantly

reduced metastasis, and overall and cancer specific mortality to an extent that was even better than in high risk patients.

Recently the AUA released notification of a BCG shortage. Unfortunately, acute shortages of BCG and other commonly used intravesical agents in the treatment of NMIBC (eg mitomycin) have become frequent. The AUA indicated that Merck is investigating a manufacturing issue and has temporarily suspended its production of TICE® BCG. (Production of Sanofi's Connaught BCG remains on hold.)

The Food and Drug Administration is working closely with U.S. suppliers

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## Underactive Bladder: a Bigger Nuisance than Overactive Bladder



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Although all urologists are familiar with overactive bladder (OAB), the inverse condition of underactive bladder (UAB) has been below the radar in our field. Yet if you know anyone struggling with underactive bladder, you are aware of the suffering

involved.

UAB is the name given to a group of troubling symptoms including hesitancy, straining, incomplete bladder emptying and frequent urination or leakage due to overflow incontinence. The symptoms and severity of UAB vary among individuals, and the course of the disease is often unpredictable. UAB is a multifactorial condition that can be caused by myogenic and neurogenic conditions as well as aging and medication side effects.<sup>1</sup>

The primary management solution of UAB is catheterization

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## Appropriate Alternatives during BCG Shortages

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to resolve issues and bring manufacturing back on line. In the interim, the Society of Urologic Oncology advised urologists to “store BCG, use alternative intravesical chemotherapy for patients with lower risk disease and prioritize patients who may benefit most from BCG therapy (ie high grade, NMIBC without previous BCG failure),” and cautioned against use of a lower dose of BCG,” despite results from EORTC 30911.

Our goal is to provide clarification and alternatives to intravesical BCG during this shortage. The importance of repeat transurethral resection (TUR) in select patients cannot be understated. Up staging of nonmuscle invasive to muscle invasive status on repeat TUR has been reported to be 24% to 29%.<sup>3</sup> Repeat TUR not only identifies patients with muscle invasive bladder cancer, but also those with high risk NMIBC who may benefit from cystectomy rather than intravesical therapies. Important high risk pathological features include lymphovascular invasion and depth of lamina propria invasion.

Cancer histology can influence the selection of patients for BCG treatment as well. Many experts caution against the use of BCG in nonurothelial histology (including squamous differentiation, glandular differentiation, nested variant and micropapillary) as worse progression-free survival after BCG has been reported.<sup>4</sup>

Despite applying several selection criteria for BCG therapy, urologists may face the circumstance of not having BCG available to administer. What are the possible alternatives in these situations?

One alternative proposed is reduced dose BCG. Oddens et al found that 1/3 dose for 3 years was not statistically inferior to full dose therapy for 1 year (recurrence-free survival 62.6% with 1/3 dose, 58.8% with full dose).<sup>5</sup> This would permit treatment of 3 times the number of patients without the risk of harm for 1 year, as long as the 1/3 dose is continued thereafter. Interferon alpha can be added to boost the cytokine response if there is concern regarding the immunologic efficacy of lower dose BCG.

Intravesical gemcitabine weekly

for 6 weeks (1 to 2 gm in 50 cc sterile water for 90 minutes) is another alternative. Some studies have followed this induction course with monthly maintenance therapy but this is often reserved for cases of BCG failure.<sup>6</sup>

[Weekly mitomycin C instillations (40 mg/20 cc normal saline) for 6 weeks followed by monthly maintenance therapy for 1 year is yet another alternative. Gemcitabine is often preferred to mitomycin C due to its lower toxicity and suggestion of improved efficacy for higher grade tumors.<sup>6</sup> Moreover, bladder irritation caused by gemcitabine acidity can be countered with 1,300 mg oral sodium bicarbonate the evening before and morning of treatment.

Valrubicin has been approved for carcinoma in situ. However, the data are not conclusive regarding its efficacy and there are also significant associated costs.

For higher risk cases or cases of BCG failure that are not cystectomy candidates, we recommend intravesical gemcitabine (1 gm/50 cc sterile water) plus mitomycin (40 mg/20 cc sterile water) instilled sequentially with dwell times of 60 to 90 minutes. A year of monthly maintenance is recommended for those who demonstrate a complete response. Preliminary published studies suggest a high response rate which is maintained at 2 years.<sup>6</sup>

We have also used a combination of intravesical gemcitabine and docetaxel which appears better tolerated than the combination of gemcitabine and mitomycin, with acceptable salvage rates even in cases of failure with BCG or other intravesical agents.

Lightfoot et al reported initial complete response rates of 75% with half of these patients maintaining a durable response to 2 years.<sup>7</sup> The protocol consists of intravesical instillation of gemcitabine (1 gm in 50 cc sterile water) for 90 minutes. After draining the bladder, immediate intravesical docetaxel instillation (37.5 mg in 50 cc sterile normal saline) is performed. The Foley catheter is removed and the patient voids approximately 2 hours later at home. Induction therapy includes 6 weekly instillations followed by monthly maintenance for 24 months. Minor toxicity of bladder irritation caused by the acidity of gemcitabine can be countered as previously mentioned. Other side effects may include

nausea and (rarely) alopecia, which are reversible.

Radical cystectomy is recommended for patients with NMIBC with high risk features (eg deep T1, variant histology) and/or recurrent high grade T1 disease who are surgical candidates. This results in the best oncologic control of disease with prolonged survival in more than 90% of patients.<sup>6</sup> The AUA and European Association of Urology recommend radical cystectomy as the preferred option for patients in whom BCG failed with limited evidence supporting the next best bladder preserving therapies.

The recent BCG shortage has been a common theme with the pharmaceutical industry having a limited supply of such agents. We must be prepared to manage these complex issues which may be more common in the future. Moreover, further comparative effectiveness research is needed to determine the appropriateness of therapy in these cases. ♦

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